PATENT
2001-1165

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Amanda Johanne KILIAAN et al. Conf. 2164

Application No. 09/703,790 Group 1651

Filed November 2, 2000 Examiner L. Barnhart

PREPARATION FOR THE PREVENTION AND/OR TREATMENT OF VASCULAR DISORDERS

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mattheus Cornelis de Wilde (insert name), hereby declare as follows:

I have read the present specification and I am familiar with the prosecution of the present application. I make this declaration in support of the present application, and to provide evidence and rebuttal of several contentions set forth in the Official Action of July 26, 2005. In particular, I declare that one skilled in the art would not be persuaded to produce the claimed preparation and practice the claimed method set forth in the present application in view of the Horrobin, Della Valle, and Fugh-Berman publications.

In particular, I have made several experiments showing that the claimed preparation and method provide an unexpectedly improved preparation and method for treating a mammal having or at risk of developing dementia syndromes, cognitive degeneration, or hearing loss.

The results are as follows:

Introduction

Aging is the predominant cause of cerebrovascular damage and resulting memory decline (Kalaria, 1996). Aged rats form no exception to this and display comparable damage to brain vasculature and also display deficits in memory (Goldman et al., 1987; de Jong et al., 1992). These deficits can be visualized using a memory function assessment task like the Radial Arm Water Maze (RAWM). The RAWM test is described in literature as a reliable, sensitive, and powerful test to assess age-related spatial learning and memory deficits (Shukitt-Hale et al., 2004). This task forms a well-accepted test to detect beneficial dietary effects on cerebrovascular damage underlying cognitive deficits.
In this experiment the intervention period lasted for three weeks. Generally, rats reach a maximum age of around 30 months. A three week intervention period in a 26-month old rat would translate to 1.5 years in a 65-year old person.

Experimental details

In this experiment the effects of 3 diets on memory performance are tested. The diets used are listed in table 1.
Diet A serves as a control diet.
Diet B is the best mode composition of dietary compositions found in Horrobin (US 4595680), della Valle et al. (US 4810497), and Fugh-Berman et al (1999). This diet comprises the optimal fatty acids levels of DHA, EPA and GLA plus citrate as found in Horrobin (example 2 no. 5), an optimal ratio of the phospholipids PS (75%) and PC (25%) at a level mentioned in della Valle example 5a, in the presence of B-vitamins and folate as found in Fugh-Berman.
Diet C is a composition providing DHA and EPA plus phospholipids

plus B-vitamins according to claims in the current application.

Table 1: Composition of the diets*.

		Diet A g/100g fat	Diet B g/100g fat	Diet C g/100g fat
Fatty acids	DHA	0,0	1,2	15,1
	EPA	0,0	1,0	3,8
	GLA	0,0	1,6	0,0
	LA	46,4	47,9	19,6
	ALA	2,3	1,0	0,7
	total w6	46,4	49,6	20,5
	total w3	2,3	3,5	21,0
		mg/100g food	mg/100g food	mg/100g food
Phospholipids	PS	0,0	55,7	16,5
	PC	0,0	16,1	107,2
	PE	0,0	18,4	0,0
	PI	0,0	12,2	0,0
		mg/100g food	mg/100g food	mg/100g food
Vitamins & minerals	folic acid	0,1000	0,1000	0,8000
	B12	0,0050	0,0050	0,0061
	B6	0,6000	0,6000	3,3000
	zinc	1,2	1,2	1,2
	citrate	0,0	200,0	0,0

* All diets have the same carbohydrates, fats and protein levels.

Eighteen aged male Wistar rats (26 months of age) were used to test the effects of dietary intervention on memory performance. The rats were fed one of the diets A, B or C throughout the experiment starting three weeks before memory assessment.

Memory performance was assessed in the RAWM (Shukitt-Hale). In the RAWM, rats have to learn the location of a hidden platform in one of the eight arms of the water maze. Thirty minutes later the rats are placed in the water again to see whether they still remember the platform location. The number of incorrect arm-

entries (errors) the rats make in finding the platform as a measure for poor memory performance.

Results

In table 2 the results of the RAWM memory test are Listed. In this test the control rats (diet A) show memory deficits. These deficits got even worse by diet B, but performance greatly improved by diet C, where the rats hardly made any errors in finding the platform.

Table 2: Results of the RAWM test for memory function.

	Diet A	Diet B	Diet C
RAWM (# of errors)	2,3	3,0	0,4

Discussion & conclusion

Diet C improved memory performance of aged rats in the test specifically designed to assess memory function (Shukitt-Hale). In contrast to this, memory performance of rats fed diet B was worse than control rats. The individual components comprising diet B all have a positive influence on memory performance and/or vasculature (Horrobin, della Valle, Fugh-Berman).

References

de Jong GI, Traber J, Luiten PG (1992) Formation of cerebrovascular anomalies in the ageing rat is delayed by chronic nimodipine application. Mech Ageing Dev 64:255-272.

della Valle F (1984) Pharmaceutical compositions and method for preparing phophatidylserine compositions useful in treating central nervous system disorders without effects on blood coagulation. US 4595680.

Fugh-Berman A, Cott JM (1999) Dietary supplements and natural products as psychotherapeutic agents. Psychosom Med 61:712-728.

Goldman H, Berman RF, Gershon S, Murphy SL, Altman HJ (1987) Correlation of behavioral and cerebrovascular functions in the aging rat. Neurobiol Aging 8:409-416.

Docket No. 2001-1165
Appln. No. 09/703,798

Horrobin DF (1988) Pharmaceutical compositions. US 4810497.
Kalaria RN (1996) Cerebral vessels in ageing and Alzheimer's disease. Pharmacol Ther 72:193-214.
Shukitt-Hale B, McEwen JJ, Saprengiel A, Joseph JA (2004) Effect of age on the radial arm water maze-a test of spatial learning and memory. Neurobiol Aging 25:223-229.

Thus, in view of the above, I declare that one skilled in the art would not be persuaded to produce the claimed preparation or practice the claimed method upon viewing the Horrobin, Della Valle, and Fugh-Berman publications.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Matthews Cornelis de Wilde
(declarant name)

February 21, 2006
(date)